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Review

Clinical challenge of diagnosing non-ventilator hospital-acquired pneumonia and identifying causative pathogens: a narrative review

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SUMMARY

Non-ventilated hospital-acquired pneumonia (NV-HAP) is associated with a significant healthcare burden, arising from high incidence and associated morbidity and mortality. However, accurate identification of cases remains challenging. At present, there is no gold-standard test for the diagnosis of NV-HAP, requiring instead the blending of non-specific signs and investigations. Causative organisms are only identified in a minority of cases. This has significant implications for surveillance, patient outcomes and antimicrobial stewardship. Much of the existing research in HAP has been conducted among ventilated patients. The paucity of dedicated NV-HAP research means that conclusions regarding diagnostic methods, pathology and interventions must largely be extrapolated from work in other settings. Progress is also limited by the lack of a widely agreed definition for NV-HAP. The diagnosis of NV-HAP has large scope for improvement. Consensus regarding a case definition will allow meaningful research to improve understanding of its aetiology and the heterogeneity of outcomes experienced by patients. There is potential to optimize the role of imaging and to incorporate novel techniques to identify likely causative pathogens. This would facilitate both antimicrobial stewardship and surveillance of an important healthcare-associated infection. This narrative review considers the utility of existing methods to diagnose NV-HAP, with a focus on the significance and challenge of identifying pathogens. It discusses the limitations in current techniques, and explores the potential of emergent molecular techniques to improve microbiological diagnosis and outcomes for patients.

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Introduction

Hospital-acquired pneumonia (HAP) is the most common healthcare-associated infection [1], affecting approximately 1.5% of hospital admissions in the UK, with similar rates in the USA [2—4]. It is associated with greater need for transfer to an intensive care setting, increased length of hospital stay [3,5], and a mortality rate of 13—30% [3,5—8]. Non-ventilated HAP (NV-HAP) accounts for two-thirds of all cases of disease [1], but most research in this field is based on ventilator-associated pneumonia (VAP) [9—12]. There are challenges in identifying cases of HAP [7,13,14], with many patients labelled as HAP not meeting the agreed criteria, and causative organisms found in only a minority of cases [15—17]. This has important implications at individual and population levels, particularly given the prominence of broad-spectrum antibiotics within treatment algorithms.

There are multiple inter-related reasons for misdiagnosis. Clinical symptoms, signs and investigations suggestive of HAP are non-specific, and gold-standard tests for diagnosis are lacking. Definitions of HAP are variable and, despite recommendations to the contrary, have frequently not distinguished between ventilated and non-ventilated patients. This review will focus on NV-HAP. It will consider current clinical practice, the relative importance of obtaining a causative organism, novel techniques to aid diagnosis, and identify gaps for further research.

Search strategy

PubMed was searched for papers referring to 'hospital-acquired pneumonia', 'HAP' or 'nosocomial pneumonia' and 'diagnosis'. Relevant additional terms for specific diagnostic methods were also included as needed. Reference lists from recent international guidelines [18,19] were screened for relevant papers. Often, results relating to NV-HAP were limited, and broader searches to include community-acquired pneumonia (CAP) and VAP were conducted.

Definitions

There is broad consensus that HAP refers to acute infection of the lung parenchyma that was not incubating at the time of admission [18]; however, there is no unified approach to identify these patients, with clinical features and thresholds varying between studies and guidelines [18—20]. This has been complicated further by frequent inclusion of VAP under the umbrella of HAP. The most recent guideline from the American Thoracic Society (ATS) recommends viewing VAP and NV-HAP as two distinct groups [19], and this review will focus on NV-HAP. As Figure 1 demonstrates, a wide variety of case definitions have been used for research looking at NV-HAP, with lack of agreement on the symptoms, signs and biochemical results required; the need for a new radiological infiltrate; and the onset time used. The studies presented are not intended to be exhaustive, but an illustrative example of the variety of definitions used and how this is currently undermining research into NV-HAP.

Diagnostic challenges

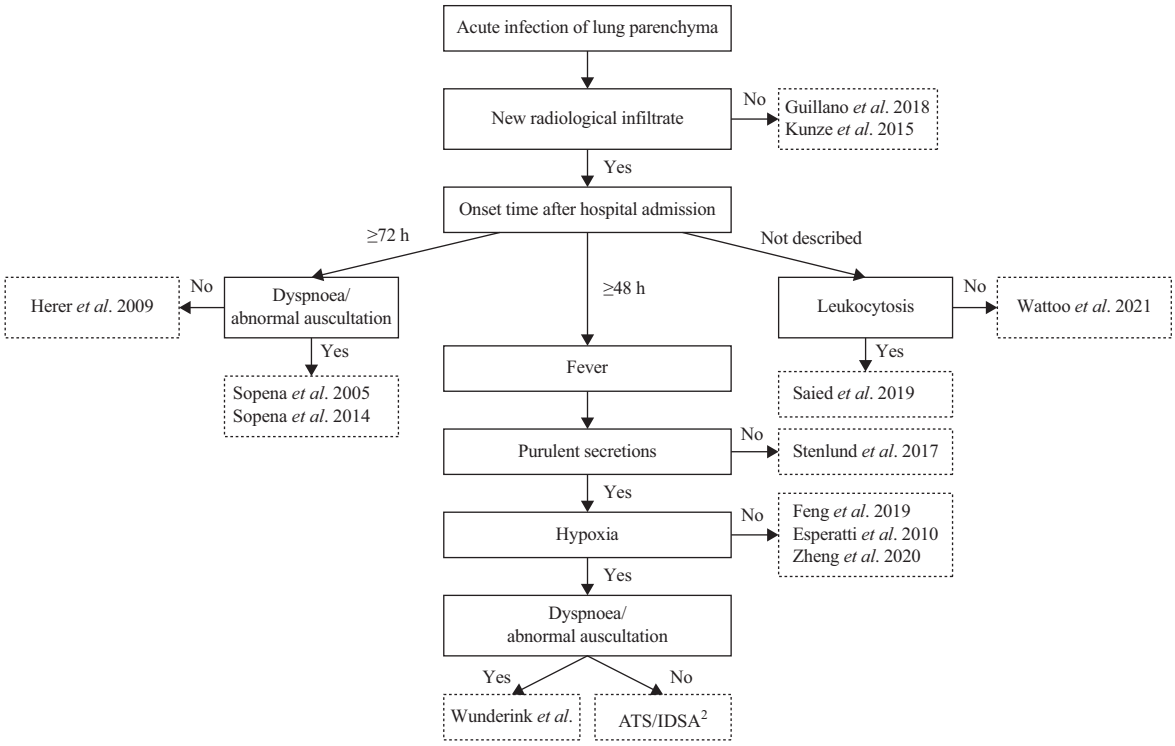
The varied definitions complicate research into NV-HAP. The ATS definition requires both 'new lung infiltrate' and 'clinical evidence that this infiltrate is of an infectious origin'; however, both aspects can be difficult to confirm.

New lung infiltrate

Studies assessing sensitivity and specificity of chest radiographs (CXR) have largely been conducted in patients with CAP or VAP rather than NV-HAP, but the results suggest low specificity (26.1% in a meta-analysis of VAP comparing CXR with histopathological results [21]). This likely represents the multiple other pathologies that can give rise to new opacification on CXR among this population. Variability in interpretation is also high [22,23], and a 'negative' CXR may have detectable infiltrates on computed tomography (CT) [24]. Where bed-bound patients have been studied specifically (where CXRs are often gained from an anteroposterior projection at the bedside), the negative predictive value of CXR is lower, at only 65%, compared with CT as the gold-standard test [25]. Radiologically confirmed NV-HAP is associated with higher rates of culture-positive sputum and higher inflammatory markers than suspected pulmonary infection with negative radiology [15]. However, while this may represent different pathological processes, it may also simply reflect differences in disease severity, with milder disease being more difficult to identify on CXR.

CT of the thorax has higher sensitivity and specificity than CXR [19], and has been used as a comparator in studies investigating other methods to diagnose pneumonia [25,26]. In CAP, the diagnostic benefits of CT, when performed routinely, have led to calls to consider CT at admission for patients with negative CXR but raised C-reactive protein (CRP), and vice versa [24].

However, CT is limited to those who can lie flat and are well enough to transfer for a scan. It also carries approximately 470 times higher ionizing radiation exposure compared with plain radiography [27], and so has historically been reserved to investigate possible complications such as empyema [28], or where CXR interpretation is uncertain [29]. Low-resolution CT (LRCT) mitigates some of this risk, with radiation exposure reducing to approximately 10 times that of CXR [30], and is well established as a screening method for lung cancer in selected populations [31—33]. LRCT has been found to have similar sensitivity to traditional CT for detecting consolidation [34], and a prospective cohort study found that LRCT changed the clinician-assessed likelihood of HAP/CAP in 45% of people who had been suspected of having pneumonia following CXR [35]. While this has potential benefits, delays in obtaining CT due to limited resources or from patients being too unwell to undergo a scan could limit the possible gains. Further, it is important to



Study	Definition
Giuliano *et al.* 2018 [3]	ICD codes
Saied *et al.* 2019 [8]	New infiltrate and one of: temperature >38.5ºC or <36.5ºC, purulent secretions, WCC >10 or <4
Sopena *et al.* 2005 [21] and Sopena *et al.* 2014 [6]	Onset >72 h of new infiltrate and two of: temperature >38ºC, purulent secretions, dyspnoea, altered auscultation, WCC >14 or <3
Stenlund *et al.* 2017 [22]	Onset >48 h of new infiltrate, fever, leukocytosis and C-reactive protein
Feng *et al.* 2019 [23]	Onset >48 h of new infiltrate, temperature >38.3ºC or <36ºC, purulent secretions and WCC >10 or <4
Wunderink *et al.* 2012 [24]	Onset >48 h of new infiltrate and two of: fever, purulent secretions, respiratory rate >30 breaths/min, hypoxia, altered mental state, abnormal auscultation, WCC >10 or leukopenia
Wattoo *et al.* 2021 [25]	New infiltrate, fever, purulent secretions and altered auscultation
Herer *et al.* 2009 [26]	Onset >72 h of new infiltrate and two of: temperature >38ºC or <36ºC, purulent secretions, and leucocytosis or leukopenia
Esperatti *et al.* 2010 [27]	CPIS ≥6, or onset >48 h of new infiltrate and two of: temperature >38ºC or <36ºC, purulent secretions, WCC >12 or <4
Kunze *et al.* 2015 [28]	Onset >48 h of 'clinical signs of pneumonia'
ATS/IDSA[2]	Onset >48 h of new infiltrate and two of: fever, purulent secretions, hypoxia and leucocytosis

Figure 1. Flow diagram of different clinical symptoms, signs and investigations used to define non-ventilator hospital-acquired pneumonia (NV-HAP) across studies and guidelines. The varying definitions used across studies and guidelines to define NV-HAP is shown first in flowchart form, with the accompanying table providing the full diagnostic criteria used for each study. The studies shown are non-exhaustive but were chosen to give examples of heterogeneity. Fever variously described, with different thresholds used. [2]Studies using the American Thoracic Society (ATS)/Infectious Disease Society of America (IDSA) (2016) definition of NV-HAP (Micek *et al.* [5], Russell *et al.* [15], Shorr *et al.* [68], Hong *et al.* [69], Messika *et al.* [73] and Ranzani *et al.* [78]). WCC, white blood cell count; ICD, International Classification of Diseases; CPIS, Clinical Pulmonary Infection Score.

consider that consolidation on CT has other causes beyond pneumonia [36], and there is a risk of misdiagnosis if it is relied upon in isolation. Again, much of the existing research has focused on CAP, and further studies on CT in NV-HAP are needed.

Ultrasound, particularly point-of-care ultrasound, is being considered increasingly as a first-line investigation in CAP [37]. Benefits include the lack of ionizing radiation, the ability to be performed at the bedside, and increasing availability in resource-poor settings [38,39]. Again, research has largely considered its utility in CAP [37,40—42] or VAP [11,43—47] rather than NV-HAP. Ultrasound has utility in diagnosing CAP in paediatric populations [48—50], facilitated by thinner chest walls and smaller lung volumes [50]. Studies in adults have also been favourable compared with CXR [40—42,51]. Several ultrasound findings support the diagnosis of VAP (Table I), but one-off examinations appear to be less useful than serial changes, which have been found to improve specificity [43,46,47]. This has implications for NV-HAP, as repeated investigations are more challenging outside of an intensive care setting. The technical ability of the operator is important, with trained but non-expert clinicians operating with less sensitivity and specificity than sonographers [52,53].

Clinical evidence of infection

As seen in Figure 1, multiple criteria are used to establish if a new infiltrate is infectious in origin. ATS lists new onset of fever, purulent sputum, leukocytosis and decline in oxygenation [19]. However, underlying conditions which increase susceptibility to NV-HAP both share and inhibit some of these clinical criteria, making them less reliable. For example, frail patients can have a weak cough and difficulty expectorating, and elderly or immunocompromised patients most vulnerable to developing NV-HAP [54] may not mount a significant inflammatory response [55,56]. It remains unclear how many of the criteria can diagnose NV-HAP optimally, but the presence of at least two criteria has been recommended [57].

In the context of VAP, these clinical factors, plus sputum culture, have been combined in the Clinical Pulmonary Infection Score (Table II) [58]. Performance of this score in patients with VAP has been limited, with meta-analysis showing pooled sensitivity and specificity of 65% and 64%, respectively [12]. To the authors' knowledge, no studies have assessed its utility in patients with NV-HAP.

Microbiology

Significance of pathogen identification

Obtaining an aetiological diagnosis has clinical impact for patients with NV-HAP, due to the variety of causative pathogens and resulting use of empiric broad-spectrum antibiotics. A global point-prevalence survey found that 25% of all inpatient antibiotic prescriptions were for healthcare-associated infections, with the most frequently prescribed being penicillin with beta-lactamase (24.8%), fluroquinolones (12.8%) and carbapenems (12.2%) [59]. A separate European survey reported that 30% of antibiotics prescribed for healthcare-associated infections had pneumonia as the indication [60]. High use of empiric broad-spectrum antibiotics not only drives antimicrobial resistance [61], but also carries a risk of adverse events for patients [62]. Despite this, a frequent challenge in NV-HAP is the limited ability to demonstrate a microbiological diagnosis, with an organism identified in under one-quarter of cases [15,16,63] (Figure 2).

Data identifying common microbiological causes of NV-HAP are limited, and undermined by the infrequency with which an organism is identified using standard techniques. Additionally, prevalence studies have often combined NV-HAP and VAP [9], or are based solely in intensive care unit populations [64,65]. With these significant limitations, NV-HAP appears to be associated with a more varied microbiological profile than CAP (as shown in Figure 2), with *Staphylococcus aureus* and Gram-negative bacteria most commonly identified, and high rates of antimicrobial resistance [63,66,67]. As a result, guidelines recommend treatment with broad-spectrum antibiotics covering both Gram-positive and Gram-negative bacteria, including *Pseudomonas* spp. [19].

Such broad coverage will not be necessary for all patients. When targeted with systematic use of multiplex polymerase chain reaction (PCR)-based techniques, viral causes are found in approximately 20% of cases of NV-HAP [68,69], and antibiotics will be ineffective [70]. Within the limitations of the multiplex PCR panels used, influenza and parainfluenza, respiratory syncytial virus (RSV) and rhinovirus were identified in

Table I
Studies comparing the sensitivity and specificity of findings on thoracic ultrasound for diagnosis of ventilator-associated pneumonia, adapted from Mongodi *et al.* [44] and Staub *et al.* [47]

Study[a]	Ultrasound finding	Sensitivity (95% CI)	Specificity (95% CI)
Mongodi *et al.* [44]	Lobar consolidation	93 (86—99)	0 (0—0)
	≥1 subpleural consolidation	81 (69—89)	41 (24—59)
	≥1 dynamic air bronchogram	44 (32—57)	81 (64—93)
Staub *et al.* [47]	Any lobar/sublobar consolidation	97 (84—99)	7 (3—18)
	≥1 subpleural consolidation	72 (55—84)	18 (8—36)
	≥1 dynamic air bronchogram	45 (29—62)	59 (40—75)

CI, confidence interval.
[a] Both studies used similar reference criteria of either a positive pathogen on quantitative culture, or all of fever, leukocytosis, increased secretions and new infiltrate on chest radiography.

Table II
Criteria used in the Clinical Pulmonary Infection Score, adapted from Pugin *et al.* [58]

Marker		Score
Temperature (ºC)	36.5–38.4	0
	38.5–38.9	1
	≥39 or ≤36	2
White blood cell count	4–11	0
	<4 or >11	1
	As above, plus band forms ≥500	2
Tracheal secretions (individual endotracheal aspirations, quantity graded as 0–4, then summated total number over 24 h)	<14	0
	≥14	1
	≥14, plus purulent	2
Oxygenation (PaO_2/FiO_2, mmHg)	>240 or ARDS	0
	≤240 and no ARDS	1
Radiography	No infiltrate	0
	Diffuse/patchy infiltrate	1
	Localized infiltrate	2
Culture of tracheal aspirate (semi-quantitative: 0, 1, 2 or ≥3)	≤1/no growth	0
	Pathogenic bacteria cultured ≥1	1
	AND also identified on Gram stain	2

ARDS, acute respiratory distress syndrome.

17%, 27%, 27% and 25% of cases, respectively [69]. Although traditionally felt to be of low pathogenicity in adults, Hong *et al.* found no difference in mortality between viral and bacterial causes of NV-HAP [69], suggesting that they may have more relevance in severe disease than previously recognized. In a number of countries worldwide, a new RSV vaccine is being deployed, with a focus on older citizens and those at greatest risk of poor outcomes from RSV [71,72]. Increasing use of molecular techniques outside of a research context may help to clarify the relative burden of viral causes and the impact of vaccination programmes, including those for viruses previously felt to be of low pathogenicity.

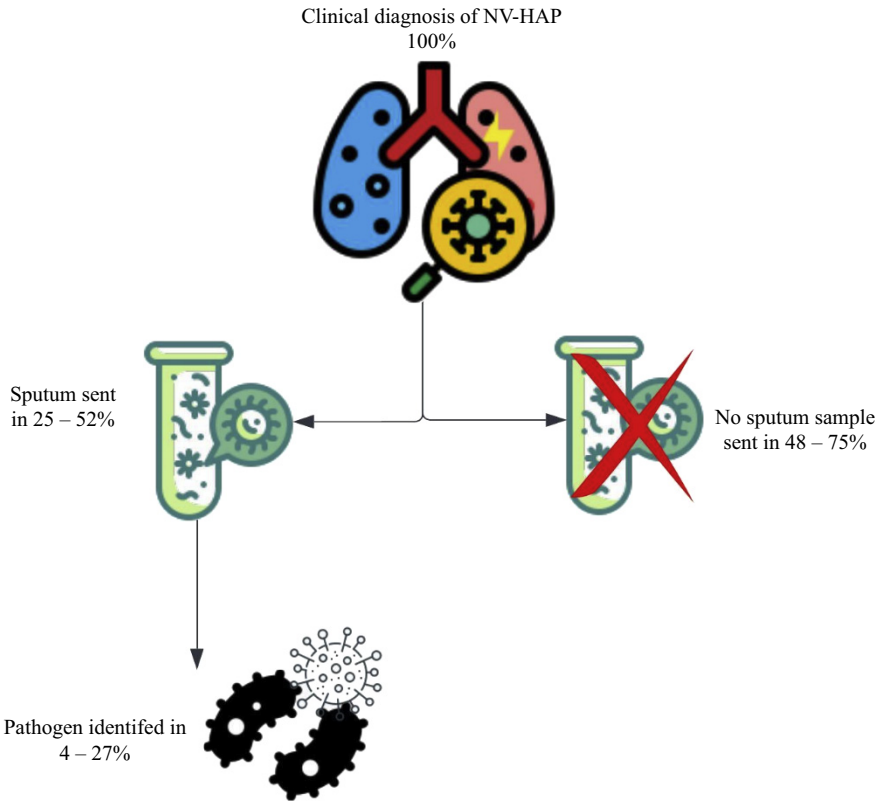
Additionally, many patients treated as NV-HAP may have an alternate non-infectious diagnosis, resulting in the unnecessary use of antibiotics. One prospective study found that 42% of cases were misdiagnosed, with at least 38% of these having a non-infectious alternative aetiology [73]. Conversely, even broad-spectrum initial empirical antibiotics may not provide sufficient cover in the presence of multi-resistant organisms, with one prospective cohort study of 110 patients with NV-HAP finding that over one-third of all organisms identified showed resistance to initial empirical antibiotics [73].

Microbiological tests in widespread clinical use

Despite the importance of identifying causative organisms, it is common for no pathogen to be isolated from clinical NV-HAP samples. In a retrospective study of 1172 patients with radiologically confirmed NV-HAP, sputum samples were obtained in only 29% of cases [16]. This was a single-centre study, but a similar rate of 24% was reported by Russell *et al.* among 166 patients treated clinically as NV-HAP [15]. The larger US study also reported that 64% of samples were inadequate due to epithelial cell counts [16]. Where sputum is sent, a substantial proportion of samples are culture negative. Literature on rates of organism identification in NV-HAP rather than VAP is limited and varies significantly. In NV-HAP, rates of 23% [5], 41–42%% [65,74] and 65% [73] have been reported, with the variability potentially arising from small sample sizes and local clinical and laboratory reporting practices. There is evidence in CAP that microbiological diagnosis from sputum culture has declined over time [75], possibly due to the increased emphasis on early empirical antibiotics, and this may also be true in NV-HAP. It is unclear what proportion of negative sputum cultures represent an absence of infection, rather than an inability to isolate the responsible pathogen. Infection may be caused by fastidious organisms that will not readily grow *in vitro*, and fungal or viral culture is not performed routinely.

Invasive approaches such as bronchoalveolar lavage or protected brush sampling improve the quantity and quality of specimens obtained in VAP [10,76,77]. These tests are not currently recommended nor practical for many patients with NV-HAP [19]; however, invasive methods were associated with an increase in microbiological diagnosis in one intensive care cohort, many of whom, while treated for NV-HAP, were subsequently intubated prior to invasive sampling being performed [78]. Of note, when focusing solely on the patients in this cohort who did not require mechanical ventilation, no significant difference in microbiological diagnosis was found compared with non-invasive methods.

Blood culture can be obtained reliably in any patient with suspected NV-HAP; however, repeated studies in both NV-HAP and VAP have shown low rates of positive samples of 5–15% [9,15,78,79] due to the low frequency of bacteraemia. Urinary antigen-based testing is widely utilized clinically within the UK for *Legionella pneumophila* and *Streptococcus pneumoniae*. With culture-based methods as a reference standard, these both have sensitivity of 70-100% and specificity >90% [80–82]. However, only *L. pneumophila* serogroup 1 tests are currently commercially available, despite other serogroups or species of *Legionella* being common in some parts of the world. Work is ongoing to develop assays with wider applicability [83]. Their



Organism	Prevalence
Staphylococcus aureus	17.0–41.4%
Pseudomonas aeruginosa	9.2–30%
Other Gram-negative bacilli *Escherichia coli* *Klebsiella* spp. *Enterobacter* spp. *Acinetobacter baumanii* *Stenotrophomonas maltophillia* *Citrobacter* spp. *Serratia* marcescens *Proteus* spp.	20.8–59.0%
Common ‘community-acquired’organisms *Streptococcus pneumoniae* *Haemophilus influenzae* *Moraxella catarrhalis*	0–14%
Fungi	2.9–8%
Viruses	1.85–22.5%

Figure 2. Prevalence of organisms identified in non-ventilator hospital-acquired pneumonia (NV-HAP), adapted from Esperatti *et al.* [65], Feng *et al.* [63], Hong *et al.* [69], Jones [67], Naidus *et al.* [16], Russell *et al.* [15], Shorr *et al.* [68], Wattoo *et al.* [66] and Weber *et al.* [113]. Sputum sampling rates based on studies with clinically diagnosed patients, utilizing non-invasive methods alone (Russell *et al.* [15], Naidus *et al.* [16] and Feng *et al.* [63]). Only two studies (Hong *et al.* [69] and Shorr *et al.* [68]) used polymerase chain reaction panels routinely to investigate for viral causes. Organisms are rarely identified in NV-HAP. When pathogens are identified, *Staphylococcus aureus* and Gram-negative bacteria are common.

benefit in NV-HAP is uncertain, as both *S. pneumoniae* and *Legionella* spp. are thought to be uncommon causative organisms [84], although cases of *Legionella* spp. are increasingly recognized [85]. Where positive, they may enable the use of targeted narrow-spectrum antibiotics. However, at present, most cases of NV-HAP are attributed to *S. aureus* or Gram-negative bacteria [66,67] for which no widespread commercial antigen testing exists.

Molecular techniques for microbiological diagnosis

Polymerase chain reaction

PCR is a laboratory technique used to amplify targeted DNA sequences. PCR-based testing is widely utilized for infectious diseases such as tuberculosis [86]. However, its use has been limited in NV-HAP and VAP. Multiplex PCR panels can assess for multiple specified organisms, and two are currently authorized by the US Food and Drug Administration for use with sputum [87,88]. Various research groups have also developed their own pneumonia panels [88,89]. Panels test for between 14 and 19 common bacteria, with some including respiratory viruses and antibiotic resistance genes [88]. However, their use remains largely limited to research settings, and the optimal role within clinical practice remains to be ascertained.

PCR offers potential benefits. Laboratory turnaround times can be reduced from days to hours [90]. They may also improve microbiological detection rates, although there are difficulties in performing gold-standard comparison studies, with a recent prospective multi-centre study showing that only 38% of positive PCR results were matched by corresponding growth on sputum culture [91]. There remains significant uncertainty regarding how to interpret this increased analytical sensitivity, and whether this represents clinically significant infection or merely colonization, given that the respiratory tract is not sterile [92]. The clinical relevance of results of the BioFire FilmArray Pneumonia Panel Plus (bioMérieux, Marcy l'Etoile, France) has been assessed recently in patients with suspected CAP and HAP (with no distinction made between ventilated or non-ventilated patients) by comparing positive samples with the likelihood of pneumonia based on a review of clinical and radiological criteria. It was found to have poor specificity, especially in suspected HAP, with an organism identified in over half of patients who were later deemed not to have pneumonia. However, meaningful interpretation of this is again limited by the lack of a gold-standard comparator, given the limitations inherent in clinical and radiological diagnosis.

Only one of the currently commercially available panels provides any quantitative information (BioFire Film Array Pneumonia Panel; bioMérieux) suggesting bacterial burden and likelihood of pathogenicity [87]. Where quantitative data are applied, it is currently unclear what thresholds should be used to indicate infection. Arbitrary cut-offs (such as $>10^5$ colony-forming units/mL estimated from a standardized dilution curve) have been applied; however, the impact of this on patient outcomes has never been assessed [89]. There is a need to investigate semi-quantitative PCR panels to help differentiate between colonization and active infection, and to better understand their clinical utility in antibiotic stewardship [93].

Metagenomic next-generation sequencing

Metagenomic methods overcome the requirements of PCR techniques to test for specific organisms, either individually or as part of a panel, by characterizing all nucleic acids present in a sample to identify any potential pathogens present, including fastidious organisms that are difficult to detect with traditional methods. With metagenomic next-generation sequencing (mNGS) methods, improvements in speed and cost make metagenomics increasingly feasible as a clinical tool. With evolving sequencing technologies, laboratory turnaround times of 24 h have been achieved clinically [94], which is an improvement on culture-based techniques. With scale and further advancement, this may reduce further; within a dedicated research setting, a turnaround time-to-result of 6 h has been achieved using bench-top long-read sequencing [95].

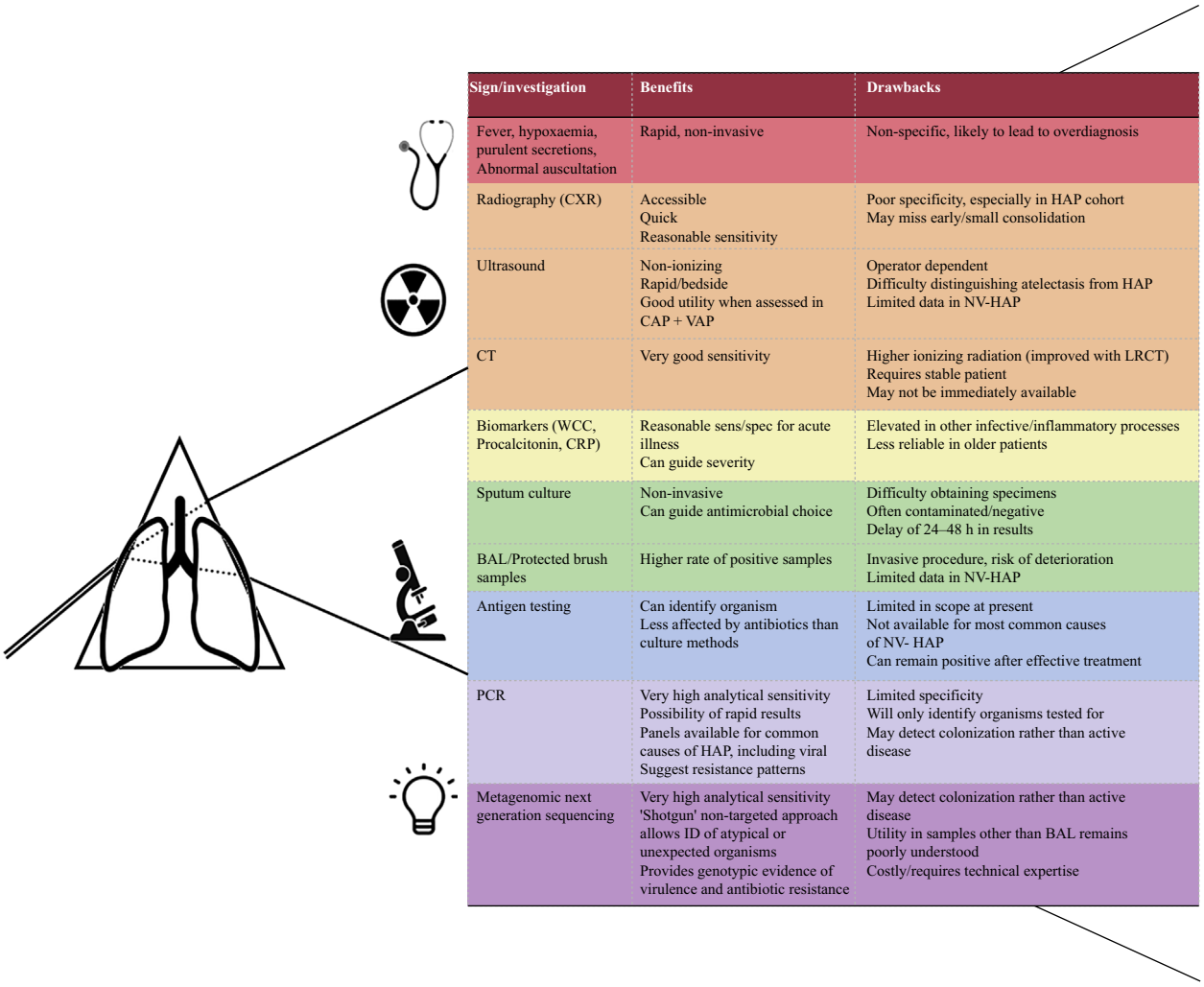
In addition to identifying pathogens, nNGS has the potential to provide information on genetic markers of antimicrobial resistance or virulence factors [96]. One retrospective study also found that mNGS is less impacted by prior antibiotic exposure than traditional culture [97]. The reasons for this are currently unclear, but it may result from identifying dead or dying bacteria in small amounts. Studies have suggested increased sensitivity, with particular benefit in identifying viral pathogens [97,98]. A meta-analysis in severe pneumonia found a presumed culpable organism by mNGS in 80% of cases, compared with 46% using traditional methods [99]. The same meta-analysis found that patients with a pathogen identified solely by mNGS had reduced length of intensive care unit admission, inpatient stay and mortality compared with patients in whom organisms were identified with traditional approaches [99]. However, this may represent disease severity and, as with PCR, uncertainty exists regarding how to interpret the findings in terms of distinguishing between colonization and active infection [100]. Most studies have assessed mNGS of bronchoalveolar lavage [98,101,102], and the use of mNGS in non-invasive sampling is less clear. In a small prospective cohort of 20 patients with severe pneumonia (no distinction made between HAP or CAP), 17 patients had a pathogen identified by mNGS of bronchoalveolar lavage, with 10 of these demonstrating concordant positive mNGS results using peripheral blood samples, despite negative traditional blood culture [103]. This offers the potential for less invasive testing using mNGS, but requires further study.

Other investigations

How best to interpret other biochemical and haematological markers of inflammation in NV-HAP is unclear. Observational studies have shown no difference in CRP between ventilated patients with and without VAP [104—106]. Procalcitonin may have utility in differentiating bacterial infection from generalized inflammation or viral infection [107], but can result in early false-negative results due to a time lag of 24—48 h [108], and neither CRP nor procalcitonin are recommended by ATS as a basis on which to start treatment [19]. Hospitalized patients are at risk of other inflammatory or infective processes that may make inflammatory markers less specific compared with a community-acquired population. Extrapolating from work in VAP is also inappropriate, as critical illness, intubation and ventilation may themselves trigger an acute phase response.

Combining complex data and the role of artificial intelligence models in NV-HAP diagnosis

With the lack of a gold-standard diagnostic test, NV-HAP requires clinicians to blend non-specific data from a variety of sources (Figure 3). This carries considerable uncertainty,



Sign/investigation	Benefits	Drawbacks
Fever, hypoxaemia, purulent secretions, Abnormal auscultation	Rapid, non-invasive	Non-specific, likely to lead to overdiagnosis
Radiography (CXR)	Accessible Quick Reasonable sensitivity	Poor specificity, especially in HAP cohort May miss early/small consolidation
Ultrasound	Non-ionizing Rapid/bedside Good utility when assessed in CAP + VAP	Operator dependent Difficulty distinguishing atelectasis from HAP Limited data in NV-HAP
CT	Very good sensitivity	Higher ionizing radiation (improved with LRCT) Requires stable patient May not be immediately available
Biomarkers (WCC, Procalcitonin, CRP)	Reasonable sens/spec for acute illness Can guide severity	Elevated in other infective/inflammatory processes Less reliable in older patients
Sputum culture	Non-invasive Can guide antimicrobial choice	Difficulty obtaining specimens Often contaminated/negative Delay of 24–48 h in results
BAL/Protected brush samples	Higher rate of positive samples	Invasive procedure, risk of deterioration Limited data in NV-HAP
Antigen testing	Can identify organism Less affected by antibiotics than culture methods	Limited in scope at present Not available for most common causes of NV- HAP Can remain positive after effective treatment
PCR	Very high analytical sensitivity Possibility of rapid results Panels available for common causes of HAP, including viral Suggest resistance patterns	Limited specificity Will only identify organisms tested for May detect colonization rather than active disease
Metagenomic next generation sequencing	Very high analytical sensitivity 'Shotgun' non-targeted approach allows ID of atypical or unexpected organisms Provides genotypic evidence of virulence and antibiotic resistance	May detect colonization rather than active disease Utility in samples other than BAL remains poorly understood Costly/requires technical expertise

Figure 3. A summary of diagnostic tests for non-ventilator hospital-acquired pneumonia (NV-HAP). There is no gold-standard test for diagnosis, instead relying on the blending of a spectrum of non-specific signs and investigations. CXR, chest radiograph; CT, computed tomography; HAP, hospital-acquired pneumonia; LRCT, low-resolution CT; WCC, white blood cell count; CRP, C-reactive protein; BAL, bronchoalveolar lavage; PCR, polymerase chain reaction.

and likely contributes to the high rates of misdiagnosis seen in practice [13,73]. The complexity of diagnosing such a heterogeneous condition based on non-specific data may be helped by machine-learning algorithms, which have been used for image interpretation [109] and to support clinical decision-making in early sepsis [110], CAP [111] and VAP [112]. However, while algorithms to aid CXR interpretation may guide NV-HAP diagnosis, these have not yet been assessed on an NV-HAP cohort, and there are no machine-learning-derived clinical decision tools specific to NV-HAP. Hospitalized patients are a rich source of data, with detailed electronic health records supplemented by frequent monitoring of blood tests and observations, allowing for algorithms to detect subtle trends. However, clinical decision support tools for NV-HAP require careful design. Simply detecting early signs of deterioration where the exact cause is unclear could exacerbate indiscriminate use of broad-spectrum antibiotics. There are also challenges in creating high-quality datasets on which to train algorithms, given the limitations with International Classification of Diseases coding data [13].

Conclusion and research gaps

Being able to diagnose NV-HAP rapidly and accurately, including any causative organisms, has important implications for patient outcomes and for effective monitoring of healthcare-associated infections. Currently, high numbers of patients have their hospital admission complicated by NV-HAP; however, the precise extent of this burden is uncertain due to difficulties identifying patients and lack of consistency in the literature regarding case definitions.

NV-HAP is a distinct entity from both CAP and VAP [19], and due to the higher number of patients affected, NV-HAP is responsible for both greater cost and total mortality than VAP [3]. Despite this, research in the NV-HAP population has been limited.

This has implications across the breadth of NV-HAP diagnosis, with a need for research to focus on:

- Establishing the role of CT and ultrasound imaging for suspected NV-HAP, with potential to improve the speed and

accuracy of initial diagnosis and reduce unnecessary use of broad-spectrum antibiotics.
- Rapid and accurate detection of pathogens, with current low rates leading to widespread empirical use of broad-spectrum antibiotics. Nucleic-acid-based techniques could improve diagnostic certainty while informing antimicrobial choice. Well-designed studies are needed to identify their optimal use and assess their impact on patient outcomes.
- The relative utility of biomarkers in establishing the presence of active infection among this cohort.
- Studies assessing the combination of clinical, radiological, microbiological and biochemical factors using machine-learning algorithms and artificial intelligence to support clinical decision-making.

To make progress on any of these issues first requires clarity in defining what is meant by NV-HAP. The ATS guidelines have been used in multiple studies; however, the lack of precision in defining clinical parameters means that, even here, there is currently potential for variation. NV-HAP is common and costly [3]. With a combination of high disease burden and marked limitations in current understanding, it is time for NV-HAP to become a serious target for future research, beginning with agreeing clear definitions.

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Conflict of interest statement

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Author contributions

SQ: writing — original draft. AL: writing — reviewing and editing. HP: writing — reviewing and editing. AA: writing — reviewing and editing. FG: writing — reviewing and editing. AM: writing — reviewing and editing. DD: supervision, writing — reviewing and editing. ES: supervision, writing — reviewing and editing. DP: supervision, reviewing and editing.

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